UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/587,512	11/08/2007	Justin Hanes	JHUC-P01-021	3582

28120 7590 02/02/2011

ROPES & GRAY LLP
IPRM - Floor 43
PRUDENTIAL TOWER
800 BOYLSTON STREET
BOSTON, MA 02199-3600

EXAMINER	
SGAGIAS, MAGDALINE K	
ART UNIT	PAPER NUMBER
1632	

NOTIFICATION DATE	DELIVERY MODE
02/02/2011	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

USPatentMail@ropesgray.com
USPatentMail2@ropesgray.com

Advisory Action Before the Filing of an Appeal Brief	Application No.	Applicant(s)	
	10/587,512	HANES ET AL.	
	Examiner	Art Unit	
	MAGDALENE SGAGIAS	1632	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 10 January 2011 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:

   a) ☐ The period for reply expires _____months from the mailing date of the final rejection.

   b) ☒ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).

5. ☐ Applicant's reply has overcome the following rejection(s): _____.

6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *1,2,5,7,8,12,13,17,18,20-22 and 26-29*.
   Claim(s) withdrawn from consideration: *3-4, 6, 9-11, 14-16, 19, 23-25*.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).

9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).

10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.

12. ☐ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). _____

13. ☐ Other: _____.

/Anne-Marie Falk/
Primary Examiner, Art Unit 1632

Continuation of 11. does NOT place the application in condition for allowance because:
The rejection of claims 1-2, 5, 7-8, 11, 13, 17-18, 20-21, 26-27 under 35 U.S.C. 103(a) as being unpatentable over Alavattam et al (US 7,060,299, filed 12/31/2003, (IDS)) in view of Norris et al (J Appl Poly Sci, 63: 1481-1492, 1997, (IDS)); Quay et al (US 7,157,426; continuation of application NO. 10/745,069, filed Dec. 23, 2003) is maintained for the reasons of record dated 11/09/2010.
Applicant's arguments have been carefully considered but fail to persuade. Applicant's substantive arguments are primarily directed to the following:

A. Applicants argue the formulas disclosed in Norris merely teach one how to calculate values of translocation permeability, the aqueous diffusion coefficient, and permeability, respectively, but do not give any indication of how to enhance the rate of particle transport in mucus. For instance, FIG. 8 of Norris shows different values of translocation permeability for microspheres functionalized with different functional groups (e.g., amidine, carboxyl, carboxylate-modified, and sulfate). As these data were obtained for particles simply having different surface functional groups, these data give no indication of what types of surface-altering agents (e.g., proteins, surfactants, sugars or sugar derivatives, nucleic acids, polymers, and other entities described in the instant specification) could be used to enhance the average rate at which the particles move in mucus as claimed. Notably, functional groups are quite different from surface-altering agents and would be expected to have different effects on the rate of transport of particles through mucus.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); In re Merck & Co., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Alavattam teaches a controlled release formulation that releases a protein at a selected rate over a period of several weeks or months. Typically, the initial burst is controlled to a selected value or is minimized while the release rate over period of time is controlled to be substantially linear (column 6, lines 27-35). Alavattam teaches the details of the present invention disclosed herein will allow those skilled in the art to adjust the rate of release to achieve a desired therapeutic effect by delivering a pharmaceutically effective amount to match a particular disease state (column 7, lines 9-16) and (ii) controlling the rate at which the proteins diffuse from the delivery device (column 8, lines 20-21) and control the protein's rate of release (column 9, lines 12-13). Alavattam suggests the use of proteins that are administered to a patient to prevent a disease such as a vaccine (column 6, lines 40-42). Norris is suggesting that hydrophobicity is also a significant factor in microsphere (MS) transport through mucin (abstract). Norris teaches the appropriate formulas for enhancing the rate of particle transport by teaching the appropriate formulas, for determining the absolute surface hydrophobicity of the polymeric particle (see p 1485, 1st column; p 1488, 2nd column; p 1489, 1st column). Given the clear suggestion by Alavattam to control the rate of release of a protein over a period of time to achieve a desired therapeutic effect by delivering a pharmaceutically effective amount to match a particular disease state, and the ability of one of ordinary skill in the art to determine the appropriate formulas for enhancing the rate of particle transport by teaching the appropriate formulas, for determining the absolute surface hydrophobicity of the polymeric particle as taught by Norris, one would have had a reasonable expectation of success. It would have been prima facie obvious to the person of ordinary skill in the art at the time the invention was made to enhance the rate of transport of a protein into a gastrointestinal mucin taught by Norris to adjust the rate of release to achieve a desired therapeutic effect by delivering a pharmaceutically effective amount to match a particular disease state as a convenient means of making the vaccine composition taught by Alavattam. The nature of the functional groups being quite different from surface-altering agents and would be expected to have different effects on the rate of transport of particles through mucus is not a limitation on all other functional groups suggested. In other words, Norris does not limit the functional groups but it teaches the translocation (PT) permeabilities of polystyrene (PS) MS with varying surface functional groups (amidine, carboxyl, carboxylate-modified [CML], and sulfate) were determined through gastrointestinal (GI) mucin while Alavattam suggests the use of proteins..

B. Applicants argue first, Alavattam does not teach or suggest the transport of particles in mucus at all; as such, the particles are not tailored to have an increased rate of transport in mucus. Second, the studies provided by Norris on particle size, surface charge, and hydrophobicity appear to be inconclusive and do not guide one of ordinary skill in the art to determine how to enhance the rate of particle transport in mucus by using surface- altering agents, e.g., as measured by translocation permeability (PT). For example, page 1491, left column of Norris states that, "while it appears that there is a relationship between the surface ionization and PT, further study is required to quantify these effects. The results shown in Figure 11 indicate that zeta-potential may not be a significant factor in determining the PT: of PS MS." [Emphasis added.]. Norris also states on page 1491 that "current results (Figure 10) also suggest that an optimal hydrophobic-hydrophilic balance may be needed to facilitate the diffusion of MS through mucin." Norris does not explain what this optimal hydrophobic-hydrophilic balance may be nor the factors that would affect this balance. For at least these reasons, one of ordinary skill in the art at the time of filing, combining the teachings of Alavattam and Norris, would have had no reasonable expectation of success in arriving at the claimed invention of independent claims 1 and 20.

In response, as discussed above given the clear suggestion by Alavattam to control the rate of release of a protein over a period of time to achieve a desired therapeutic effect by delivering a pharmaceutically effective amount to match a particular disease state, and the ability of one of ordinary skill in the art to determine the appropriate formulas for enhancing the rate of particle transport by teaching the appropriate formulas, for determining the absolute surface hydrophobicity of the polymeric particle as taught by Norris, one would have had a reasonable expectation of success. It would have been prima facie obvious to the person of ordinary skill in the art at the time the invention was made to enhance the rate of transport of a protein into a gastrointestinal mucin taught by Norris to adjust the rate of release to achieve a desired therapeutic effect by delivering a pharmaceutically effective amount to match a particular disease state as a convenient means of making the vaccine composition taught by Alavattam. The nature of the functional groups being quite different from surface-altering agents and would be expected to have different effects on the rate of transport of particles through mucus is not a limitation on all other functional groups suggested. In other words, Norris does not limit the functional groups but it teaches the translocation (PT) permeabilities of polystyrene (PS) MS with varying surface functional groups (amidine, carboxyl, carboxylate-modified [CML], and sulfate) were determined through gastrointestinal (GI) mucin while Alavattam suggests the use of proteins..

C. Applicants argue while Quay teaches a variety of mechanisms to improve the transport characteristics of biologically active agents such as proteins across hydrophobic mucosal membrane barriers, there is no teaching, suggestion or motivation in Quay that the same methods for transporting biologically active agents alone would work for biologically active agents that are associated with a particle, such that the average rate at which the particle moves in mucus would be enhanced by at least five- fold. Therefore, the results of the modifications asserted in the Office Action would not be predictable from Quay, or the combination of Alavattam, Norris, and Quay, and thus the proposed combination does not render the instant claims obvious. For example, page 7 of the Office Action points to the teachings in Quay that surface-active agents can be incorporated within mucosal delivery formulations, and that these classes of surface-active agents typically include solubilization of the biologically active agent. While these surface- active agents may allow increased transport of biologically active agents by solubilizing them to prevent aggregation of the biologically active agents, Quay does not teach or suggest that these biologically active agents and surface-active agents could be used with a polymeric particle. Furthermore, the skilled worker at the time of filing would not have been able to predict whether the mechanism of action that increases the rate of transport of the biologically active agent in mucus (e.g., by preventing aggregation of the biologically active agent) would apply when both the biologically active agent and surface-active agent are associated with a polymeric particle as claimed. Thus, the combination of the teachings in Quay with the particles disclosed in Alavattam would not lead to a reasonable expectation of success.

In response, Quay is not cited for the teachings a polymeric particle for the transport of a biologically active agent or surface-active agents because Alavattam provides the teachings for a polymeric particle by teaching "biologically active protein" in the PLGA microparticles includes proteins and polypeptides that are administered to patients as the active drug substance for prevention of or treatment of a disease or condition as well as proteins and polypeptides that are used for diagnostic purposes, such as enzymes used in diagnostic tests or in vitro assays as well as proteins that are administered to a patient to prevent a disease such as a vaccine (column 6, lines 39-46).

D. Applicants argue the Examiner on page 7 of the Office Action also points to the teachings in Quay that surfactants can be used to improve the transport characteristics of selected biologically active agents by surface charge modification (e.g., by cationization) of biologically active agents. Quay does not teach or suggest that these surface charge-modified biologically active agents could be combined with polymeric particles. Moreover, one of skill in the art at the time of filing could not have predicted that this mechanism for increasing the rate of transport of biologically active agents would be effective when the biologically active agent is associated with a polymeric particle as claimed, since the particle would be substantially larger than the biologically active agent alone as taught in Quay. Thus, the combination of the teachings in Quay with the particles disclosed in Alavattam would not lead to a reasonable expectation of success.

In response, Quay teaches small molecule drugs for enhanced delivery across hydrophobic mucosal membrane barriers, by surface charge modification of selected biologically active agents or delivery-enhancing agents described herein [0139] (claim 8). Given the clear suggestion by Alavattam to control the rate of release of a protein over a period of time to achieve a desired therapeutic effect by delivering a pharmaceutically effective amount to match a particular disease state, and the ability of one of ordinary skill in the art to determine the appropriate formulas for enhancing the rate of particle transport by teaching the appropriate formulas, for determining the absolute surface hydrophobicity of the polymeric particle as taught by Norris, it would have been prima facie obvious to the person of ordinary skill in the art at the time the invention was made to use a small molecule in order to enhance the rate of transport of a protein into a gastrointestinal mucin taught by Norris to adjust the rate of release to achieve a desired therapeutic effect by delivering a pharmaceutically effective amount to match a particular disease state as a convenient means of making the vaccine composition taught by Alavattam.

E. Applicants argue Quay's use of mucoadhesive polymers to yield enhanced permeation effects. As the name suggests, "mucoadhesive" polymers adhere to mucus. Applicant does not see how the combination of such polymers with the bioactive small molecule agents disclosed in Quay would lead one of ordinary skill in the art to expect that such mucus adhering polymers would increase the transport of polymeric particles in mucus as claimed.

In response, Quay is not teaching that the particle moves through mucus at a 5-fold enhanced rate, however, since Alavattam teaches a composition with all three components comprising a polymer core, a bioactive agent and a surface-altering agent disposed on the surface of the core then the composition inherently has the property of moving through mucus at a 5-fold enhanced rate. Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. See In re Ludtke 441 F.2d 660, 169 USPQ 563 (CCPA 1971). Whether the rejection is based on "inherency" under 35 USC 102, or "prima facie obviousness" under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products. In re Best, Bolton, and Shaw, 195 USPQ 430, 433 (CCPA 1977) citing In re Brown, 59 CCPA 1036, 459 F.2d 531, 173 USPQ 685 (1972) and In re Fitzgerald, 619 F.2d 67, 70, 205 USPQ 594, 596 (CCPA 1980) (quoting In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433-34(CCPA 1977)).
There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of invention, but only that the subject matter is in fact inherent in the prior art reference. Schering Corp. v. Geneva Pharm. Inc., 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003). "Products of identical chemical composition can not have mutually exclusive properties." A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Applicant is referred to MPEP 2112 for further discussion on inherency. Thus, the rejection is maintained.

The rejection of claims 1, 12 is rejected under 35 U.S.C. 103(a) as being unpatentable over Alavattam et al (US 7,060,299, filed 12/31/2003 (IDS)) in view of Norris et al (J Appl Poly Sci, 63: 1481-1492, 1997 (IDS)); Quay et al (US 7,157,426; continuation of application NO. 10/745,069, filed Dec. 23, 2003) and further in view of Singh et al, (PNAS, 97(2): 811-816, 2000, (IDS) is maintained for the reasons of record dated 11/09/2010.
Applicant's arguments are directed to the asserted combination of Alavattam in view of Norris and Quay.
In response, the same rebut apply here as discussed above. Thus, the rejection is maintained.

The rejection of claims 1, 22 is rejected under 35 U.S.C. 103(a) as being unpatentable over Alavattam et al (US 7,060,299, filed 12/31/2003, (IDS)) in view of Norris et al (J Appl Poly Sci, 63: 1481-1492, 1997, (IDS)); Quay et al (US 7,157,426; continuation of application NO. 10/745,069, filed Dec. 23, 2003) and further in view of Baichwal et al (U.S. Patent No. 5,612,053 (IDS)) is maintained for the reasons of record dated 11/09/2010.
Applicant's arguments are directed to the asserted combination of Alavattam in view of Norris and Quay.
In response, the same rebut apply here as discussed above. Thus, the rejection is maintained.

Claims 1, 28-29 is rejected under 35 U.S.C. 103(a) as being unpatentable over Alavattam et al (US 7,060,299, filed 12/31/2003, (IDS)) in view of Norris et al (J Appl Poly Sci, 63: 1481-1492, 1997, (IDS)); Quay et al (US 7,157,426; continuation of application NO. 10/745,069, filed Dec. 23, 2003) and further in view of Dawson et al (Vet Rec, 127(13):338, 1990) is maintained for the reasons of record dated 11/09/2010.
Applicant's arguments are directed to the asserted combination of Alavattam in view of Norris and Quay.
In response, the same rebut apply here as discussed above. Thus, the rejection is maintained..